

### **REMARKS**

Applicants have amended claims 42 and 47 to include that the quenching substance suppresses at least some of the signal from unbound labeled reagent and that determination of the analyte is performed or effected without physical separation as recommended by the Examiner. New claims 48-59 have been added. Support for new claims 48, 53 and 59 can be found, for example, on page 7, second paragraph to page 8, first full paragraph. Support for new claim 58 can be found, for example, on page 5, second full paragraph, and on page 7, first full paragraph. Support for new claims 49 and 54 can be found, for example, on page 6, third full paragraph. Support for new claims 50 and 55 can be found, for example, on page 8, first full paragraph. Support for new claims 51, 52, 56, and 57 can be found, for example, on page 9, first full paragraph. The present amendment also corrects errors of minor character in the specification. No new matter has been added. Applicants respectfully request entry of the amendments and new claims.

### **Rejection under 35 U.S.C. 112, Second Paragraph**

The Examiner rejected claims 2-7, 9-16, 19, 21, 23, 33-36, 42-45, and 47 as allegedly indefinite for reciting the phrases "capable of" and "the determination occurs." The Examiner also alleged that the phrase "suppressing signal from unbound labeled reagent" in step (a) of claims 42 and 47 confused her and requested clarification.

Applicants respectfully disagree with the Examiner's position and submit that the meaning of the phrases "capable of" and "the determination occurs" are clear to a person of ordinary skill in the art upon reading the specification. However, solely to expedite prosecution, Applicants have amended claims 42 and 47 to include that a "determination is performed or effected" in accordance with the Examiner's suggestion.

In response to the Examiner's request for clarification of step (a) in claims 42 and 47, Applicants submit that in at least one embodiment, binding between the labeled

reagent and the analyte causes the quenching substance to quench or suppress at least some of the signal originating from unbound labeled reagent. In view of the amendments, Applicants submit that the claims are clear to one of ordinary skill in the art. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on 35 U.S.C. § 112, second paragraph.

**Rejections Under 35 U.S.C. § 102(e)**

The Examiner rejected claims 2-4, 6, 7, 9-13, 35, 42-45, and 47 under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 6,361,944 (Mirkin) or U.S. Patent No. 6,667,179 (Selvin). Applicants respectfully traverse these rejections.

For a rejection to be sustained under 35 U.S.C. §102(e) each and every element of the claims must be disclosed in the cited prior art reference. The present claims include the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation (*e.g.*, washing, filtering, separation layers) of bound and unbound label.

Mirkin discloses methods of detecting nucleic acids using labeled nanoparticle-oligonucleotide conjugates that hybridize to complementary oligonucleotide targets. (see, for example, Mirkin col. 6, lines 42-67). Mirkin requires physical separation (*e.g.*, washing) of bound and unbound labeled oligonucleotides:

After the binding oligonucleotides are bound, unbound binding oligonucleotides are *washed* from the substrate.

(Mirkin, at col. 23, lines 57-59, emphasis added);

The nanoparticle-oligonucleotide conjugates are contacted with the binding oligonucleotide bound to the substrate under conditions effective to allow hybridization of the binding oligonucleotide to the oligonucleotides on the nanoparticles. After the nanoparticles are bound, unbound nanoparticle-oligonucleotide conjugates are *washed* from

the substrate.

(Mirkin, at col. 23, line 63 to col. 24, line 2, emphasis added);

An alternate method for easily visualizing the assay results is to spot a sample of nanoparticle probes hybridized to a target nucleic acid on a glass fiber filter . . . while drawing the liquid through the filter. Subsequent rinsing with water *washes the excess, non-hybridized probes through the filter*, leaving behind an observable spot comprising the aggregates generated by hybridization of the nanoparticle probes with the target nucleic acid ...

(Mirkin, at col. 20, lines 42-51, emphasis added);

Following hybridization, unbound nanoparticle-oligonucleotide conjugates are *washed* from the substrate.

(Mirkin, at col. 25, lines 65-67, emphasis added); and

When monitored by fluorescence, the detection method described above proved to be **difficult** due to background fluorescence from the membrane. This problem was overcome by “*washing*” the latex microspheres by centrifugation to remove excess gold nanoparticle probes before spotting an aliquot on a reverse-phase TLC plate.

(Mirkin, at col. 59, lines 28-33, emphasis added).

Clearly Mirkin calls for physical separation of bound and unbound label. Moreover, Mirkin does not disclose a solid phase coated with a quenching substance that suppresses at least some signal from unbound labeled reagent. Rather, the nanoparticles of Mirkin (*e.g.*, gold colloidal particles) have “high extinction coefficients that give rise to their beautiful color... and produce an immediate color change visible to the naked eye...” (Mirkin, at col. 16, lines 64 to col. 17, line 7). Thus, the nanoparticles or solid phase of Mirkin actually generates signal, and does not suppress it as claimed in the

present application. Accordingly, Mirkin does not disclose each and every element of the claims and Applicants request that this rejection under 35 U.S.C. §102(e) be reconsidered and withdrawn.

Regarding Selvin, Applicants respectfully submit that Selvin does not qualify as prior art under 35 U.S.C. § 102(e). The present application claims priority to German application No. 19903576, filed January 29, 1999. In the Office Action dated June 22, 2001, the Examiner acknowledged Applicants' priority claim. The filing date of Selvin is October 28, 1999, which is after the priority date for the present application. Thus, Selvin does not qualify as prior art under 35 U.S.C. § 102(e). Accordingly, Applicants request reconsideration and withdrawal of the rejection based on the Selvin reference.

#### **Rejections Under 35 U.S.C. § 103(a)**

The Examiner rejected claims 5, 14-16, 21, 23, 33, 34, and 36 under 35 U.S.C. §103(a), for allegedly being obvious over Mirkin and U.S. Patent No. 6,121,055 (Hargreaves). Applicants respectfully traverse this rejection.

The Examiner alleged that it would have been obvious to combine the method disclosed in Mirkin with the wells disclosed in Hargreaves, since the Hargreaves wells are allegedly an obvious modification of well configurations known in the art. The Examiner conceded that both Mirkin and Hargreaves differ from the present claims in failing to disclose specific volumes and well configurations, but asserted that these well configurations are allegedly well known in the art.

Applicants respectfully disagree. To establish a *prima facie* case of obviousness, all of the claim elements must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991). Applicants refer the Examiner to the arguments made above regarding the Mirkin reference. Mirkin is directed to labeled nanoparticle-oligonucleotide conjugates and requires physical separation (*e.g.*, washing, filtering, etc.) of bound and unbound label. Further, Mirkin does not disclose, teach or suggest coating a solid phase with a quenching substance that suppresses at least some

signal from unbound labeled reagent as presently claimed.

Hargreaves does not disclose, teach, or suggest the present claims. Hargreaves discloses physical separation (*e.g.*, washing, filtration, separation layers or centrifugation) of bound and unbound label. Hargreaves at col. 11, lines 46-50:

In heterogeneous binding assays, **the primary layer serves to separate bound from unbound label** by allowing the penetration of binding components without allowing the penetration of unbound label (emphasis added).

The primary layer that the Examiner asserts separates bound from unbound label, requires physical separation techniques such as centrifugation. See for example, Hargreaves at col. 6, lines 39-48:

For homogeneous assays, additional embodiments are employed. In one such embodiment, the density of the entire assay mixture may be greater than the density of the primary layer. Such an embodiment typically utilizes a barrier layer or primary layer which is in a solid or gel form during assay initiation, but which is displaced by the assay mixture during a subsequent **centrifugation step** (emphasis added).

Clearly Hargreaves calls for physical separation of bound and unbound label. Moreover, Hargreaves does not disclose coating a solid phase with a quenching substance that suppresses at least some signal from unbound labeled reagent. Accordingly, Hargreaves cannot render the presently claims obvious.

Neither Mirkin nor Hargreaves alone or in combination disclose, teach or suggest the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation (*e.g.*, washing, filtering, separation layers) of bound and unbound label. Further, no motivation is stated in Hargreaves or Mirkin to combine these two references as suggested by the Examiner. Accordingly, the claims cannot be considered obvious and Applicants respectfully request withdrawal of the rejection.

The Examiner also rejected claim 19 as allegedly obvious in light of Mirkin, Hargreaves, and U.S. Patent No. 5,381,224 (Dixon). The Examiner conceded that neither Mirkin nor Hargreaves disclose obtaining a measurement signal by a spatially staggered measurement. However, the Examiner alleged that Dixon discloses obtaining spatially staggered measurements by measuring a luminescence spectrum at each pixel position, and that it would be obvious to use staggered measurements disclosed in Dixon in combination with the method of Mirkin as modified by Hargreaves.

Applicants respectfully disagree with the Examiner. Applicants refer the Examiner to arguments made above regarding Mirkin and Hargreaves. Applicants submit that Dixon does not disclose, teach, or suggest the present claims, alone or in combination with Mirkin and/or Hargreaves. Dixon discloses scanning optical imaging of macroscopic specimens, which is said to allow both confocal and non-confocal imaging in reflected light, as well as photo-luminescence, fluorescence and other contrast mechanisms. See col. 3, lines 10-20. Dixon does not teach or suggest the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation of bound and unbound label. In fact, Dixon does not mention quenching substances at all. Since Dixon does not teach or suggest the present claims, this reference cannot render the present claims obvious.

Applicants submit that, assuming Mirkin, Hargreaves, and Dixon are combined, they do not disclose, teach, or suggest the present claims. Further, no motivation is stated in Dixon, Mirkin, and/or Hargreaves to combine these references. Accordingly, for these reasons and for the reasons stated above, Applicants request reconsideration and withdrawal of the rejections based on Mirkin, Hargreaves, and Dixon.

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### **Conclusion**

In view of the amendments and remarks herein, reconsideration and allowance are respectfully requested.

No fee is believed to be due with respect to the filing of this amendment and reply. If any fees are deemed due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,



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